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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,268	10/05/2001	Peter R. Baum	3101-A	4855

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,268	BAUM ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,61-66 and 68-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59, 61-66, 68-112 and 114* is/are rejected.

7)☒ Claim(s) *113 and 115* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/05 has been entered.

2. Claims 59, 61-66, 68-115 are pending and under examination in the instant application.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 112 and 114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The specific amino acid residues claimed in claims 112(a-w), and claim 114(a-x), represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 8/10/05 does not point to the specification for support for the specific amino acid residues as claimed in claims 112(a-w) and claim 114(a-x). However, the specification does not provide a clear support of such limitations. The instant claims now recite limitations, which were not clearly disclosed in the specification and recited in the claims as originally filed.

7. Claims 59, 61-66, 68-112 and 114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189-250 and 287-342, and SEQ ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration; does not reasonably provide enablement for any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of

SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73; any substantially purified polypeptide comprising any amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amion acid identity across the length of amino acids 58-404 of SEQ ID NO:4 or 6 in clai 79, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of amino acids 58 through 404 of SEQ ID NO: 4 or 6 in claim 80; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 86, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95%, or 99% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 87; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12 or 31 in claim 93, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12, or 31 in claim 94; any isolated polypeptide of claim 93 produced by a process comprising (a) culturing a recombinant host cell comprising any "polynucleotide" having nucleotide sequence encoding said polypeptide and (b) isolating said polypeptide in claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising a polynucleotide having a nucleotide sequence encoding said polypeptide or The polypeptide of claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising any polynucleotide having any nucleotide sequence encoding said polypeptide, wherein said nucleotide sequence is selected from the group consisting of nucleotide4s 172-1026 of SEQ ID NO:3, 5, 9 or 11; nucleotides 172-1212 of SEQ ID NO:3 or 5, and nucleotides 172-1098 of SEQ ID NO: 9 or 11 in claim 102; wherein said polypeptide comprises an amino acid sequence selected from the group consisting of (a) amino acids 58-342 of SEQ ID NO: 4, 6, 10, 12 or 31, (a) amino acids 58-404 of SEQ ID NO:4 or 6, (c) amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, (d) amino acids 74-404 of SEQ ID NO:4 or 6, (e) amino acids 58 through 365 of SEQ ID NO:10, 12, or 31 and (f) amino acids 74-365 of SEQ ID NO:10, 12 or 31 in claim 105, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell into which a polynucleotide comprising a nucleotide sequence encoding said polypeptide has been introduced in claim 111, wherein said polypeptide "comprises an amino acid sequence recited in claims 112 and 114. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 3/22/05.

Applicant's arguments, filed 8/18/05, have been fully considered, but have not been found persuasive.

Applicant traverses the rejection based on the use of term "comprising" which leaves the claims open for inclusion of unspecified amino acids on either or both sides of the N- and C-terminal of the core structure of nectin-3 polypeptide. Applicant asserts that the specification discloses that the amino acid sequences of 58-404 of SEQ ID NO: 4 or 6 (human nectin 3α) and 58-366 of SEQ ID NO: 12 (human nectin 3β). Applicant draws the Examiner's attention to Examples 4-6 wherein a polypeptide (i.e., nectin-3α-Fc of SEQ ID NO: 13) comprising amino acid residues 58-404 of SEQ IDN Os: 4 or 6 (human nectin 3α) and including amino acid residues 74-365 of human nectin 3β of SEQ ID NO: 12) is being used. Further, Applicant further contends that within the group of acknowledged enabled sequences the "core structure" is coupled to a host of N- and/or C-terminal extensions of various lengths and complexity including: complete signal sequences, signal sequences lacking N-terminal amino acid residues, signal sequences with murine substituted sequences, transmembrane domains, cytoplasmic domains, Fc regions form human IgG1, and small peptide affinity tags such as FLAG and His tags. Applicant concludes that since the core structure has demonstrated independent biological activity, the N- and C-terminal extensions of these enabled sequences cannot be considered to interfere with the function of the "core structure of nectin-3". Applicant contends that the Office Action provides no evidence to indicate that any other similar N- or C- terminal extensions would negate the demonstrated biological activity of the "core structure".

However, it is noted that the pervious Office Actions state that SEQ ID NO: 13 used in examples 4-6 is enabled. Further, the pervious Office Action states that the sequences comprising the complete signal sequences (i.e., SEQ ID NOS: 6 and 10), signal sequences lacking N-terminal amino acid residues (SEQ ID NOs: 2 and 8), signal sequences with murine substituted sequences (i.e., SEQ ID NOs: 4 and 10), transmembrane domains, cytoplasmic domains, Fc regions form human IgG1(i.e., SEQ ID NOs: 13 and 14), and small peptide affinity tags such as FLAG and His tags (i.e. SEQ ID NOs: 15 and 16) are enabled. Further, Applicant's argument regarding the function of core structure of nectin-3, is not recited in the claims and does not address the rejection at hand.

Applicant further argues that assuming arguendo, that an extension, such as a peptide tag or linker, adversely affected the biological activity, the tagged or linkerd polypeptide would still be useful for raising antibodies, either by immunization with the complete peptide fusion or with proteolytic fragments thereof. Production of antibodies using small peptide immunogens, including monoclonal antibodies, is routine in the art and discloses in Applicants' specification at pages 23-24.

The Examiner notices that that the previous Office Actions states that the claimed sequences are enabled for "inhibiting endothelial cell migration". The Examiner notes while the specification discloses how to make antibodies to fragments, however, fails to disclose a use for the resultant antibodies to the small peptide immunogens. The Examiner acknowledged that it is routine in the art to make antibodies to a peptide fragment, however, the use of the resultant antibody has to be specific. Since the same can be done with any peptide fragment, the asserted use of the peptide fragments is not specific to the nectin-3 fragments.

With respect to the "at least about 80%-99% sequence identity polypeptide", applicant appears to inquire about how identifying differs from finding the sequences. Applicant explains that one of skill in the art, using only a pencil and paper and the sequences provided in a Applicants' invention, can produce a list of sequences having the required identity to Applicant's claimed sequences. Applicant contends that mere substitution of three alanine residues for any three amino acid residues within the sequence of amino acid residues 58-404 creates a sequence that is 99% identical across the length of that sequence as required by Applicants' claimed invention. Further, Applicant submits that known sequences can be compared to the sequence of amino acid residues 58-404 of SEQ ID NOs: 4 or 6, for example, to determine whether or not the sequence is about 80-99% identical over the length of the claimed sequence. Applicant further points to the previous response regarding computer programs and algorithms are known in the art and commercially available for making such determinations and are described within applicants' specification. Applicant concluded that one of skill in the art can easily and quickly determine whether any sequences in question would fall within the scope of the sequences of the claimed invention. As such, the sequences are now found.

However, any assay for finding a product is not equivalent to a positive recitation of how to make such a product. The fact pattern fails to disclose any particular structure for the claimed at least about 80%-99% sequence identity polypeptide. The specification does not provide any guidance or any working examples in this unpredictable art, thus the artisan would have been unable to make the claimed compound without undue experimentation.

With respect to statement in the previous Office Action that " the specification fails to provide sufficient guidance as to which amino acid of SEQ ID NO: 4, 6, 10, 12 and 31 are essential for maintaining the biological activity and which changes can be made in the structure of SEQ ID NO: 4, 6, 10, 12 and 31 and still maintain function", Applicant argues hat the claims are directed to polypeptides having at least 80% amino acid identity across the length of amino acid residues 58-404, not across the entire sequence of SEQ ID NOs: 2, 3, 6, 8, 10, 12 and 31. Applicant submits that the skilled artisan may rely on various tools and skills when analyzing sequences, for example, alignment of the sequence in question with homolgous sequences to determine which residues are conserved and where substitutions, deletions, additions are made and tolerated. Applicant points to table 2 of the instant specification provides such an alignment of related nectin sequences identifying conserved residues and providing such an alignment of related nectin sequences identifying conserved residues and providing a consensus sequence. Assays are provided to confirm the endothelial cell migration inhibition activity of the polypeptides.

However, the art acknowledges that function cannot be predicted based solely on structural similarity and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Further, the amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)). As mention in the previous Office Action

that since the core structure of the nectin 3 polypeptides is a key determinant of activity of nectin 3, residue substitutions that are conservative can have severe phenotypic effects. However, there is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. Further, it is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. The specification does not teach which changes in core structure of nectin 3 amino acids of SEQ ID NOs: 4, 6, 10, 12, 31 would not alter all the activities of the polypeptides. Therefore, the specification fails to provide sufficient guidance as to which amino acid of the core structure of SEQ ID NOs: 4, 6, 10, 12, 31 is essential for maintain its biological activity and which changes can be made in the core structure of SEQ ID NOs: 4, 6, 10, 12, 31 and still maintained the same function.

Applicant further points to Examples 5-6 regarding the previously stated statement "while experimental testing techniques using cell adhesion compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure." Applicant contends that polypeptides of the claimed invention were shown to have inhibitory properties. Endothelial cell migration assays are routinely used to characterize proteins or polypeptides of interest. Applicant contends that a search of the term: endothelial cell migration" on medline turns up hundreds of references that describe use of endothelial cell migration assays to identify related biological activities of proteins and polypeptides. Applicant contends that such assays have been used to screen large numbers of unrelated proteins to determine which have the desired activity and would be the subject of further experimentation.

However, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of core structure of nectin 3 polypeptides encompassed by the instant claims would be inhibit endothelial cell migration.

8. Claims 59, 61-66, 68-78, 112 and 114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed 6/4/04.

Applicant is in possession of a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189 to 250 and 287 to 342, and SEQ ID NO:13-16 wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration.

Applicant is not in possession of any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ

ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73.

Applicant's arguments, filed 8/18/05, have been fully considered, but have not been found persuasive.

Applicant points to Examples 3-6 of the specification for abundant description of the correlation or relationship between the structure of the invention, the core structure of nectin 3 and it's inhibition of endothelial cell migration, as well as other activities. Applicant asserts that the specification describes a correlation or relationship between the structure of the invention, the core structure of nectin 3 (amino acid residues 58-404 of SEQ ID NO:s 4 or 6 including aa 74-365) and it's inhibition or endothelial cell migration function, a feature deemed essential to the instant invention.

However, the essential feature is not claimed, and therefore the arguments are irrelevant to the claimed invention.

Applicant contends that without some evidence to the contrary, one of skill in the art could envision the claimed genus of polypeptides comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 (which includes amino acid residues 74-365).

While the Examiner acknowledged that the claims recite the structure of a polypeptide comprising amino acid residues 58-404 of SEQ ID NOS:4 or 6 (which includes amino acid residues 74-35), however the functional correlation or relationship between the structure of the invention, the core structure of nectin 3 (amino acids 58-404 of SEQ ID NOs: 4 or 6) and it's inhibition of endothelial cell migration function is not claimed. As pointed by Applicant response in Examples 3-6 the core structure (aa 58-404 of SEQ ID NOs: 4 or 6) is required to the inhibition of endothelial cell migration.

Applicants further submit that they provided a structural feature that is common to the genus made up of polypeptides possessing amino acid residues 58-404 or 74-365 which are identical in the structure set forth in SEQ ID NOs: 4, 6, 10, 12 and 31 (i.e., nectin 3α, 3β and 3γ).

However, no correlation or relationship between the structure of the invention, the core structure of nectin 3 (aa 58-404 of SEQ ID NOs: 4 or 6) and it's inhibition of endothelial cell migration is claimed for the skilled artisan to envisage the claimed genus of polypeptides comprising said core structure of nectin 3 which retain the features essential to the instant invention.

9. No claim is allowed.

10. Claims 113 and 115 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 5, 2005

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